Negative regulation of Shh levels by Kras and Fgfr2 during hair follicle development.

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Public Summary:
Hair follicle growth is negative affected by the RAS signaling pathway. In this study, we discovered that RAS and FGF inhibit the production of critical hair growth factor called SHH. SHH is involved in hair growth and hair cycle activation. A better understanding of the molecular signaling pathways in hair activation and growth may provide new ways to treat hair loss and potentially stem cell diseases in other tissues.

Scientific Abstract:
Activating mutations in the KRAS oncogene are associated with three related human syndromes, which vary in hair and skin phenotypes depending on the involved allele. How variations in RAS signals are interpreted during hair and skin development is unknown. In this study, we investigated the developmental and transcriptional response of skin and hair to changes in RAS activity, using mouse genetic models and microarray analysis. While activation of Kras (Kras(G12D)) in the skin had strong effects on hair growth and hair shape, steady state changes in downstream RAS/MAPK effectors were subtle and detected only by transcriptional responses. To model the transcriptional response of multiple developmental pathways to active RAS, the effects of growth factor stimulation were studied in skin explants. Here FGF acutely suppressed Shh transcription within 90min but had significantly less effect on Eda, WNT, Notch or BMP pathways. Furthermore, in vivo Fgfr2 loss-of-function in the ectoderm caused derepression of Shh, revealing a role for FGF in Shh regulation in the hair follicle. These studies define both dosage sensitive effects of RAS signaling on hair morphogenesis and reveal acute mechanisms for fine-tuning Shh levels in the hair follicle.

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